

Prenatal versus postnatal priming of allergen specific immunologic memory: The debate continues

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The question of when sensitization to environmental allergens is initiated—that is, before or after birth—has attracted the attention of successive generations of researchers dating back to the early 1900s,¹ and our group has contributed data to both sides of this debate over the last decade as the recent chapters in this complex story have unfolded.^{2,3} The importance of gaining a clear resolution to this issue is clear: knowledge of the timing of initial sensitization helps to define the potential window for implementation of primary prevention therapies, and importantly helps in the framing of advice to parents regarding allergen exposure of their at-risk offspring. In the current issue of the Journal, Pfefferle et al⁴ offer new data on the presence of allergen specific IgE in cord blood from ~29% of a birth cohort, findings that are consistent with a string of studies going back to the 1980s. Attempts to use these earlier findings to develop prognostic indices of risk for future atopy development have been unsuccessful, because elevated cord blood IgE displays high specificity (>95%) but disappointingly low sensitivity ($\leq 15\%$) as a prognostic index at the population level.⁵ However, the exceptionally high specificity of this link with risk for future atopic disease justifies ongoing investigations into underlying mechanisms.

At the heart of the debate surrounding cord blood IgE is the issue of its origin. It is widely believed that the presence of this antibody generally connotes maternal contamination during delivery, given that IgE is not actively transported across intact placental membranes. In the study by Pfefferle et al,⁴ the authors have adopted the strategy of using IgA as a surrogate marker of maternal contamination, because this antibody class also is not transferred transplacentally.⁶ Using a cutoff of 32 $\mu\text{g/mL}$ IgA as an index of maternal contamination, the authors demonstrate that the bulk of the CB samples fall below this range and contend therefore that attendant IgE in cord blood is likely to be of fetal origin. This may be correct, but other interpretations cannot be discounted. For example, others have argued that a lower IgA cutoff (10 $\mu\text{g/mL}$) should be applied to be certain of excluding maternal contamination.⁶ Second, IgA is valid as a control in this situation only if it is catabolized in the fetus or at a rate comparable to IgE, but this information is not available. An additional

potential complication relates to the possibility that there may be mechanisms other than simply leakage of whole (maternal) blood for transplacental translocation of the 2 classes of antibody. In particular, it is well recognized that the peripheral blood of patients with food allergy contains immune complexes that are composed predominately of IgG:allergen but that also include specific IgE (see review⁷), and the likelihood that the IgA cutoffs proposed would be sufficiently sensitive to detect translocation via this pathway is difficult to determine. It is pertinent to note in this context the observation of Pfefferle et al⁴ of strong association between maternal and fetal food allergen-specific (as opposed to inhalant specific) IgE.

The potential for active transport of allergen:IgG-containing complexes across the placental barrier has been clearly demonstrated in the elegant studies of Szepefalusi et al,⁸ and given the strong adjuvant properties of specific IgG in relation to antigen processing, these complexes could provide a source of immunogen for the priming of fetal T_H cells that are a prerequisite for initiation of local IgE production. Specific IgE has also been identified as a potent antigen-focusing agent for optimization of sampling of allergens by antigen-presenting cells,⁹ and its presence in the fetal compartment would theoretically provide an additional and stronger adjuvant stimulus for T-cell priming, which in this microenvironment must rely on infinitesimally small amounts of translocated allergen. The fetal immune system does appear capable of priming T_H2 immunity if given a sufficiently strong stimulus, as demonstrated in the parasite literature.¹⁰ However, whether this actually happens in the context of less potent immunogens, such as environmental allergens, still remains controversial.

An alternative approach to this same question taken by many researchers has involved a direct focus on the development of allergen-specific T_H cell populations themselves. Dating back to early 1990s, the presence of allergen-responsive T cells in cord blood has been reported by multiple different groups (see review¹¹), and the fetal origin of these putative T_H-memory cells was established using a combination of cloning and genotyping techniques.³ However, more recent studies¹² suggest that these allergen-responsive fetal T cells are not conventional primed T_H-memory cells, but instead represent a transitional population between thymocytes and adult T cells.^{12,13} These T cells are known as recent thymic emigrants, and although they are immunologically naive, they can engage with (and be accordingly activated by) a broad spectrum of foreign antigens via low-affinity receptors that lack the fine specificity of antigen receptors on conventional CD4⁺ T_H cells.¹² These recent thymic emigrants dominate the peripheral T-cell compartment in mouse and human being during the neonatal period¹³ and provide the developing immune system with the means to generate T-cell cytokine signals (likely to assist in activation of intracellular pathogen killing mechanisms in phagocytes) quickly at

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sites of antigen encounter, in the absence of conventional T-memory cells.¹² They are programmed to die rapidly by apoptosis after cytokine release, preventing them from contributing to local pathology. They can be rescued by exposure to appropriate cytokines,¹² but it is not known whether they can persist thereafter at the periphery for extended periods. Likewise, it is not known whether the cytokines they release after activation can contribute to local IgE B-cell switching in the neonate, but there is no *a priori* reason to doubt this possibility. It is intriguing to note in this context that the B-cell compartment in neonates is dominated by an equivalent of these immature recent thymic emigrants—CD5⁺ B cells with low-affinity receptors exhibiting a preimmune repertoire that precedes initial antigen contact.¹⁴ The possibility that interactions between transplacentally translocated allergen and these immature neonatal T-cell and B-cell populations could generate transient IgE response merits further exploration.

In summary, the study by Pfefferle et al⁴ adds further to the ongoing debate on whether primary allergic sensitization is initiated before or after birth, but as per earlier studies, it falls short of a final resolution. However, this article represents only 1 of the early stages in a unique prospective birth cohort study in which it is planned *inter alia* to track IgE responses over a period of years. In a similar (albeit smaller) study cohort, we have recently prospectively tracked allergen-specific T_H-cell responses in individual children from cord blood through age 2 years via serial sampling, and observed that stable responsiveness, which is predictive of future sensitization, did not develop until at or beyond 6 months of age.³ The larger PASTURE cohort⁴ provides an ideal study population for similarly tracking the fate of allergen-specific IgE in the cord blood of individual children, and information on the ensuing waxing or waning of antibody titers over the period of the first 6 to 12 months of postnatal life, when available, may provide a much clearer answer to this important question.

REFERENCES

1. Rosenau M, Anderson J. A study of the cause of sudden death following the injection of horse serum: hereditary transmission of the susceptibility of guinea pigs. *Hyg Lab Bull* 1906;29:73-9.
2. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998;160:4730-7.
3. Rowe J, Kusel M, Holt BJ, Suriyaarachchi D, Serralha M, Hollams E, et al. Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. *J Allergy Clin Immunol* 2007;119:1164-73.
4. Pfefferle P, Serdar S, Ege MJ, Büchele G, Bluemer N, Krauss-Etschmann S, et al. Cord blood allergen-specific IgE is associated with reduced IFN- γ production by cord blood cells: The Protection against Allergy—Study in Rural Environments (PASTURE) study. *J Allergy Clin Immunol* 2008;122:711-6.
5. Hattevig G, Kjellman B, Björkstén B. Clinical symptoms and IgE responses to common food proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987;17:571-8.
6. Ownby DR, McCullough J, Johnson CC, Peterson EL. Evaluation of IgA measurements as a method for detecting maternal blood contamination of cord blood samples. *Pediatr Allergy Immunol* 1996;7:125-9.
7. Carini C. IgE immune complexes in food allergy: significance, pathogenicity and clinical considerations. *Clin Allergy* 1987;17:485-97.
8. Szepefalusi Z, Loibichler C, Pichler J, Reisenberger K, Ebner C, Urbanek R. Direct evidence for transplacental allergen transfer. *Pediatr Res* 2000;48:404-7.
9. Maurer D, Ebner C, Reininger B, Fiebigler E, Kraft D, Kinet JP, et al. The high affinity IgE receptor (Fc epsilon RI) mediates IgE-dependent allergen presentation. *J Immunol* 1995;154:6285-90.
10. Malhotra I, Mungai PL, Wamachi AN, Tisch D, Kioko JM, Ouma JH, et al. Prenatal T cell immunity to *Wuchereria bancrofti* and its effect on filarial immunity and infection susceptibility during childhood. *J Infect Dis* 2006;193:1005-13.
11. Holt PG, Sly PD. Prevention of adult asthma by early intervention during childhood: potential value of new generation immunomodulatory drugs. *Thorax* 2000;55:700-3.
12. Thornton CA, Upham JW, Wikstrom ME, Holt BJ, White GP, Sharp MJ, et al. Functional maturation of CD4+CD25+CTLA4+CD45RA+ T regulatory cells in human neonatal T cell responses to environmental antigens/allergens. *J Immunol* 2004;173:3084-92.
13. Hassan J, Reen DJ. Human recent thymic emigrants: identification, expansion, and survival characteristics. *J Immunol* 2001;167:1970-6.
14. Casali P, Notkins AL. CD5+ B lymphocytes, polyreactive antibodies and the human B-cell repertoire. *Immunol Today* 1989;10:364-8.